Armed Forces College of Medicine

AFCM

Applied Biochemistry MSK Module

ILO:

- Correlate clinical cases of musculoskeletal system to their biochemical basis

The enzyme dopamine β-hydroxylase which catalyses conversion of dopamine to norepinephrine requires

(A) Vitamin A
(B) Vitamin C
(C) Vitamin E
(D) Vitamin B12
(E) Vitamin K

Describe regulation of glycogen metabolism

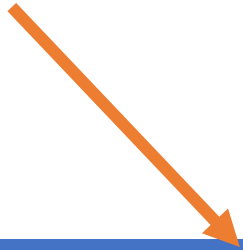
1. Allosteric Control

* **Glycogen synthase:**
  - **Stimulated by G-6-P & ATP**
  - **Inhibited by glycogen (product)**

* **Glycogen Phosphorylase**
  - **Stimulated by AMP (muscle).**
  - **Inhibited by glucose and ATP.**

2. Covalent Modification

Glycogen synthase



Activated by de-phosphorylation

Glycogen Synthase a

Inactivated by phosphorylation

Glycogen Synthase b

Glycogen phosphorylase

Activated by phosphorylation

Glycogen phosphorylase a

Inactivated by de-phosphorylation

Glycogen phosphorylase b

Uridine diphosphate glucose (UDPG) is:

(A) Required for metabolism of fructose
(B) Product of puruvate dehydrogenase
(C) A substrate for glycogen synthetase
(D) A substrate for glycogen phophorylase

What is glycogenin?

- **It is the protein primer for glycogen synthesis**

About 8 glucose residues linked by α 1 -4 glucosidic linkages & -Attached to protein called Glycogenin

- **The active form of glycogen …….is phosphorylated, the active form of glycogen ……..is dephosphorylated**

- a) Hydrolase, dehydrogenase
- b) Dehydrogenase; hydrolase
- c) Hydrolase; semisynthase
- d) Phosphorylase; synthase
- e) Synthase; phosphorylase

- **What is type of bond done by glycogen synthase enzyme?**

α 1-4 glycosidic bond

- **What is type of bond done by branching enzyme?**

α 1-6 glycosidic bond

Which of the following enzymes is not involved in glycogen degradation ?

a)Glucose 6 phosphatase

b)Phosphorylase

c)Amylo (1-4) to (1-4) glucan transferase

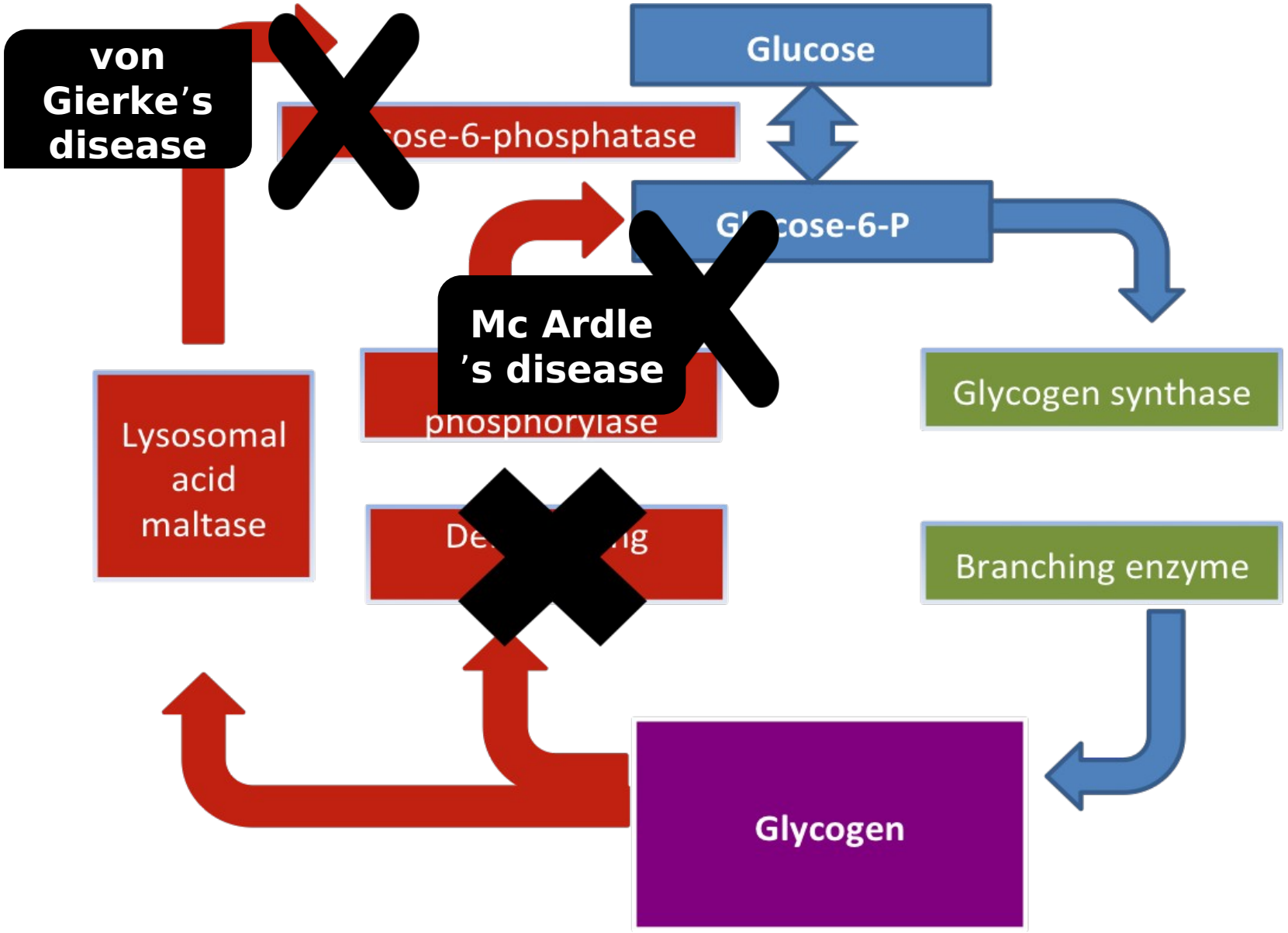
d)Amylo (1-4) to (1-6) glucan transferase

e)Phosphoglucomutase

- **Which of the following enzyme generates free glucose during breakdown of glycogen in skeletal muscle ?**

- **α-1,6 glucosidase**

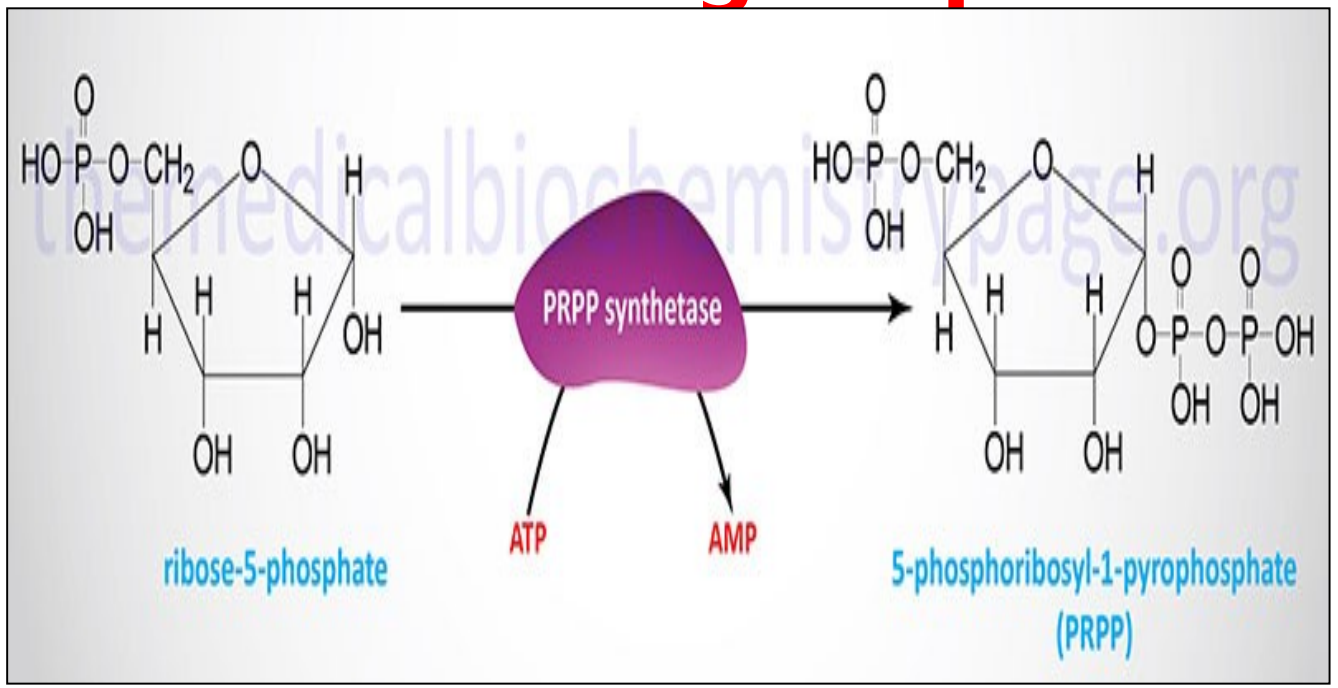
Mention the most important glycogen storage disease


von Gierke's disease
Glucose
ose-6-phosphatase
cose-6-P
Mc Ardle 's disease
Lysosomal acid maltase
phosphorylase
Glycogen synthase
Branching enzyme
Glycogen

- **Mention the characteristic feature of Von Gierke‘s Disease**

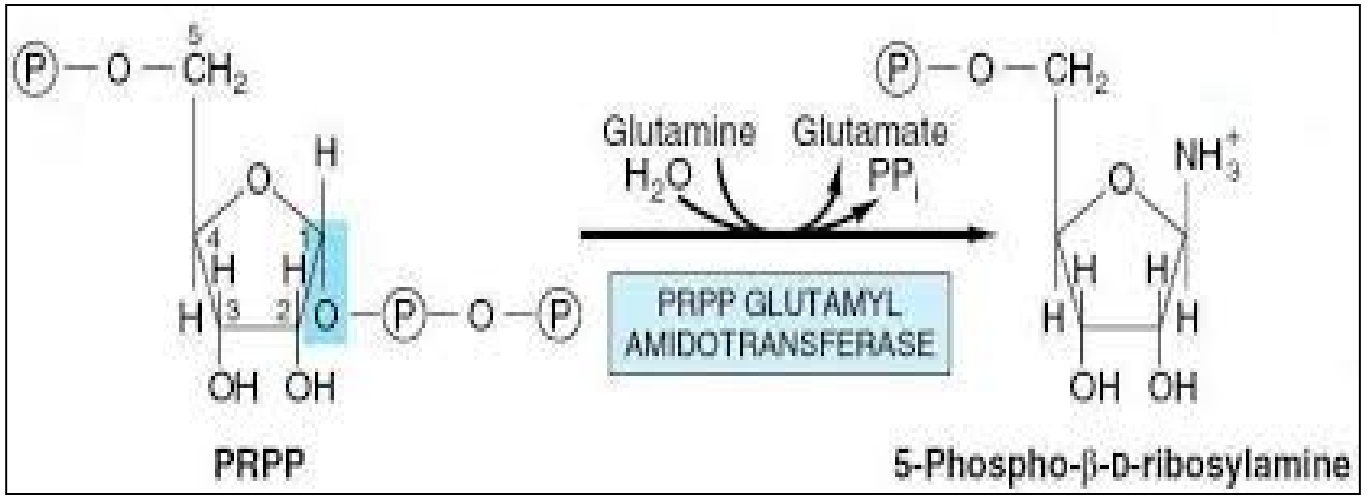
1. **Fasting hypoglycemia & lactic acidosis**
2. **Hepatomegaly**
3. **Hyperlipidemia & ketosis .**
4. **Hyperuricemia with gouty arthritis**

- **Describe the first two steps in purine synthesis and which is the rate limiting step?**



2-Second Step

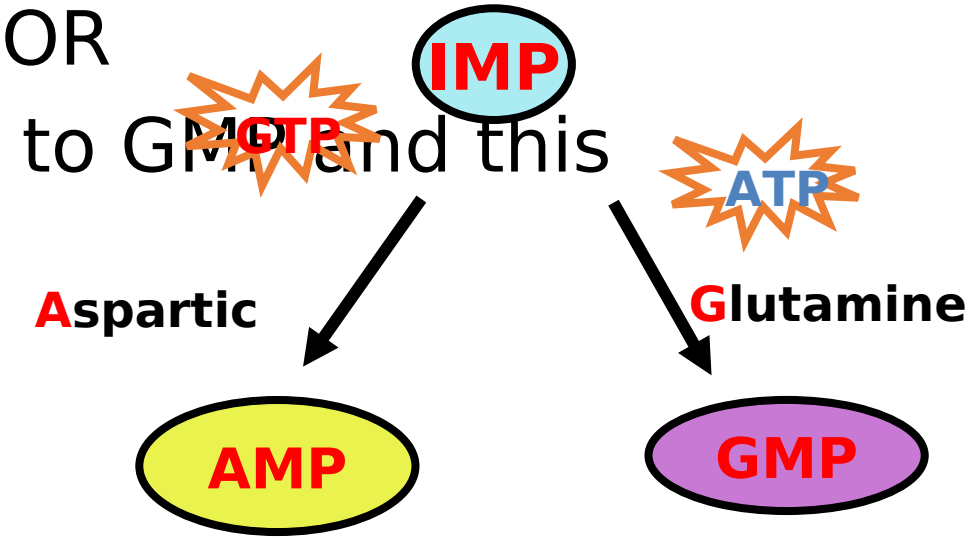
It is done by : Glutamine PRPP amidotranseferase



It is the rate limiting step

- **What is the "Reciprocal control"?**
- The first nucleotide synthesized is **IMP** (inosine monophosphate) ..this requires 6 ATP.

1. IMP is converted to AMP and this consumes GTP OR
2. IMP is converted to GMP and this consumes ATP



- **Describe the biochemical basis of the following drugs:**

a) **Sulfonamides**

B) **Methotrexate**

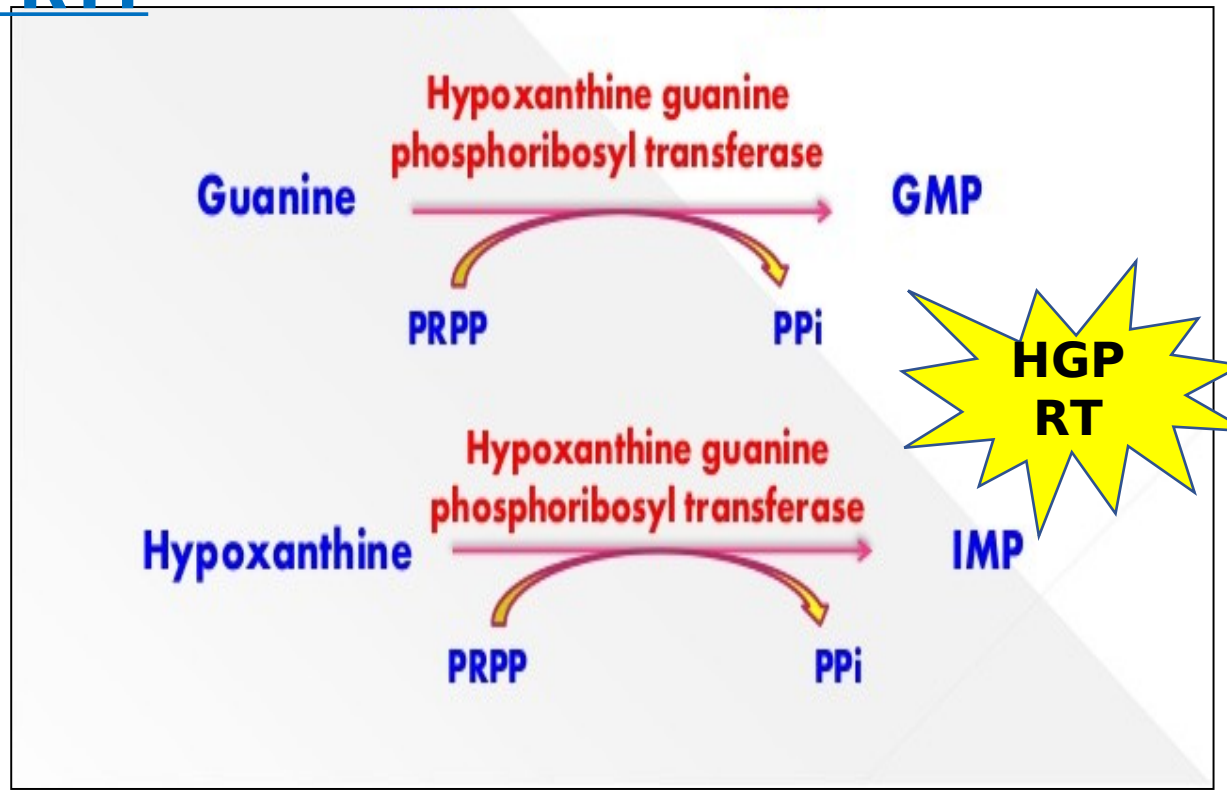
c) **6- mercaptopurine**

A) **Sulfonamides antibiotics inhibit bacterial synthesis of folic acid** ***(folic acid is needed for purine synthesis in bacteria).***

B) **Methotrexate is structural analog of folic acid is used as anticancer drugs as it inhibits dihydrofolate reductase**

C) **6- mercaptopurine is structurally similar to IMP, so used as anticancer** ***(competitive inhibitor for conversion of IMP to either AMP or GMP)***

Describe the biochemical action of HGPRT?



Thioredoxin is involved in the:

A. conversion of AMP to ATP.

B. conversion of dUMP to dTMP.

C. conversion of a ribonucleotide to a deoxyribonucleotide.

D. inhibition of xanthine oxidase as a treatment for gout.

E. degradation of nucleoprotein.

Direct sources of purine ring atoms in the de novo synthesis of IMP include:
1. glutamine.
2. a component of the tetrahydrofolate
3. aspartate.
4. glycine.

A. 1, 2 and 3
B. 1 and 3
C. 2 and 4
D. 4 only
E. All four

case

- **64 year old man has a painful, swollen right big toe. The symptoms began two days earlier. There is no history of trauma. His joint aspirate shows pus cells and no organisms. Laboratory analyses indicate an elevated serum uric acid level and urate crystals in his urine**

- **What is the diagnosis?**
- **What is the genetic causes o this disease ?**

Gout

2-Over-production of uric acid

Defect of one or more of enzymes of purine synthesis

1- Genetic defect of PRPP synthetase (responsible for purine synthesis) So purines are synthesized in excess and degraded to uric acid

2-Lesch- Nyhan syndrome: a genetic defect in HGPRT leads to inability to reuse purines and so they are degraded to uric acid.

What is (“orange sand”) sign?

- In infants earlier urate crystal formation leads to the presence of orange colored deposits (“orange sand”) in the diapers of infants with this disorder.

- This may be the first manifestation of Lesch-Nyhan syndrome,

MCQ

Allopurinol is used in treatment of gout as it:

A. Increases secretion of uric acid

B. Is competitive analogue to hypoxanthine.

C. Decreases activity of PRPP.

D. Decreases urinary reabsorption of uric acid.

E. Is competitive analogue to Adenine.

- **Which of the following would NOT be expected to contribute to hyperuricemia (gout)?**

A. **Unusually high levels of PRPP.**
B. Inhibition of xanthine oxidase.
C. Unusually high turnover of nucleic acids.
D. High activity of adenosine deaminase.
E. Deficiency of HGPRT.

- **Allopurinol is an inhibitor of xanthine oxidase. Administration of allopurinol to a patient with gout can lead to all of the following EXCEPT:**

- A. decreased pain in big toe
- B. decreased urate in the urine.
- C. an increase of hypoxanthine in the blood.
- D. increased levels of PRPP .
- E. increased xanthine in the blood.

- **Adenosine deaminase (enzyme) deficiency is associated with:**
- A. Severe combined immunodeficiency (SCID)
- B. X-linked agammaglobulinemia
- C. Transient hypogarnmaglobulinemia of infancy
- D. Chronic granulomatous disease

- Adenosine deaminase deaminates adenosine to:

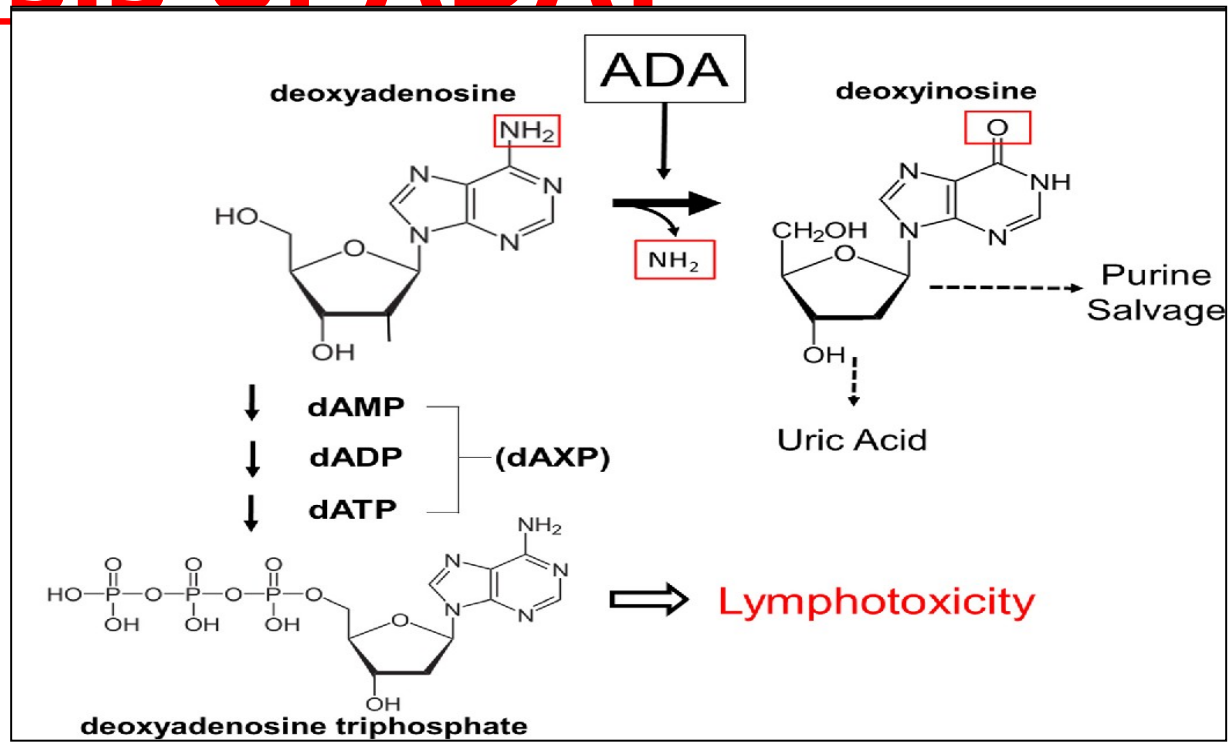
a) Hypoxanthine

b) Inosine

c) Xanthine

d) Guanosine

What is the biochemical basis of ADA?



Case scenario

A 4-year-old boy was brought for consultation for hematuria, edema of lower extremities as well as swollen right leg. He was the 12the born in a poor family, where one previous child died from malnutrition and dehydration in the period of infancy. The child was fed only with cow's milk and biscuits.

At admission the baby was afebrile, pale, and malnourished; his hair was dry and cracked. Clinical evaluation showed no organomegaly, no neurological signs, gingival bleeding

http://www.namrata.co/case-study-scurvy

Case scenario

Laboratory findings were as follows

Red Blood Cell Count 3.5 million/mm^3

Hemoglobin (Hb) 7 g/dl

Haemtocrit (Hct) 30%

Serum Iron low

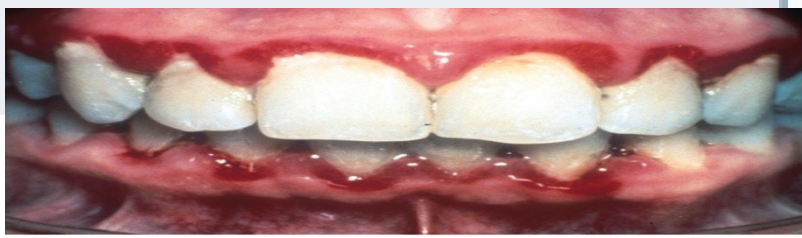
Liver function...

Ultrasound of kidney was

?What is the suspected diagnosis

Doppler of blood vessels of both legs was normal which excluded thrombophlebitis. Swelling of the right leg indicated radiological investigation. Massive subperiosteal hematoma on the right femur, dilatated metaphyses and general osteoporosis had been present on the radiogram.

What is the probable diagnosis for this child ?



Why this vitamin is deficient in this boy?

What are the functions of vitamin C

Functions of vitamin C

A]Cofactor for hydroxylases enzyme (reducing agent in hydroxylation reaction

1) Hydroxylation of proline and lysine in collagen synthesis → normal connective tissue (collagen) formation.

(2)Hydroxylation reactions in corticosteroid biosynthesis

(3) Bile acid formation (7 α-hydroxylase step).

(4) Tyrosine catabolism and synthesis of norepinephrine and epinephrine.

B] Vitamin C reduces ferric (Fe^{+++}) to ferrous ion (Fe^{++}) in stomach and thus helps absorption of iron.

[C] Vitamin C acts as an antioxidant

antioxidant vitamins are: (vitamins C, E, and β-carotene)

Prevention of chronic disease

D] Immunological function

E] Prevention of chronic diseases

Explain on Biochemical basis vitamin C is useful in common cold and viral infection

D) Immunological function Of vitamin C

Vitamin C is thought to moderate colds by :

- Enhancing many immune cell (such as some leukocyte) functions and increase phagocytic function phagocytosis of virus or bacteria
- Destroying histamine, which causes many of a cold's symptoms.
- Increase immunoglobulin's synthesis

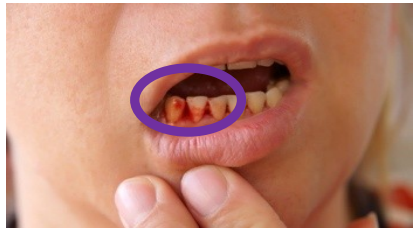
https://cdn.images.express.co.uk/img/dynamic/11/590x/Cold-symptoms-update-750878.jpg

Vitamin C Deficiency (scurvy):

due to decreased fresh fruit and vegetables in diet

Manifestations :

[A] Manifestations due to impaired hydroxylation of proline and lysine in collagen

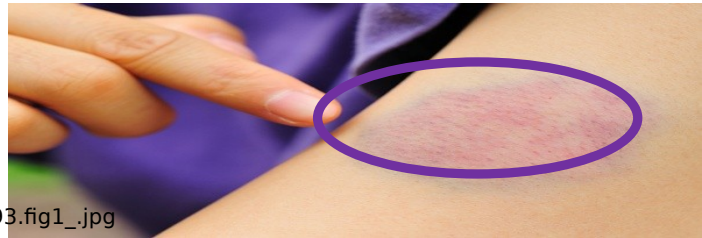


(1) Delayed wound healing.
(2) loose teeth & sore and spongy gums bleeding gums.

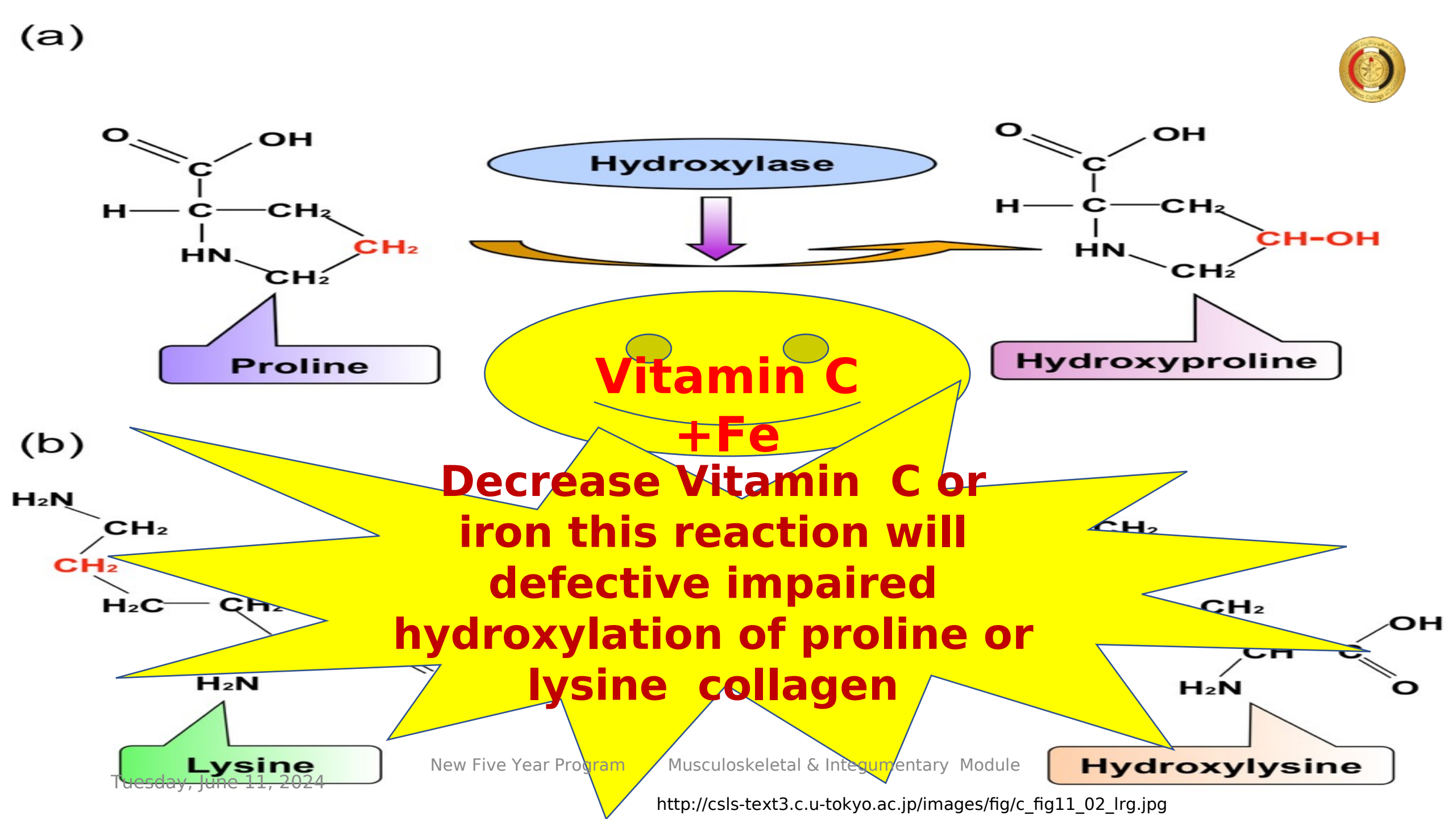
(3) Swollen joints & Osteoporosis: due to inability to maintain collagenous matrix of bone → easy fracture

(4) Easy bruising and subcutaneous hemorrhage

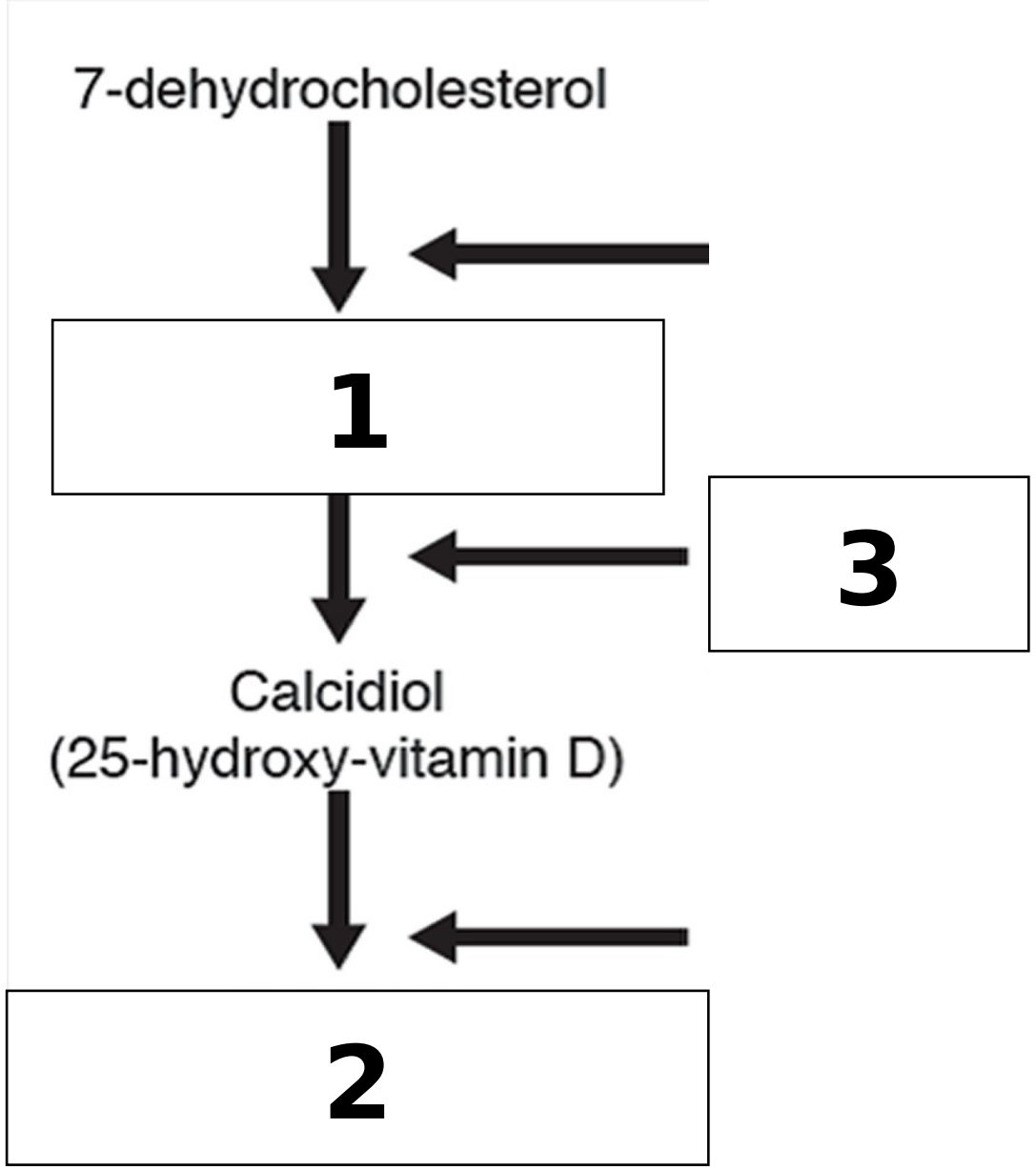
This is due to increase capillary fragility

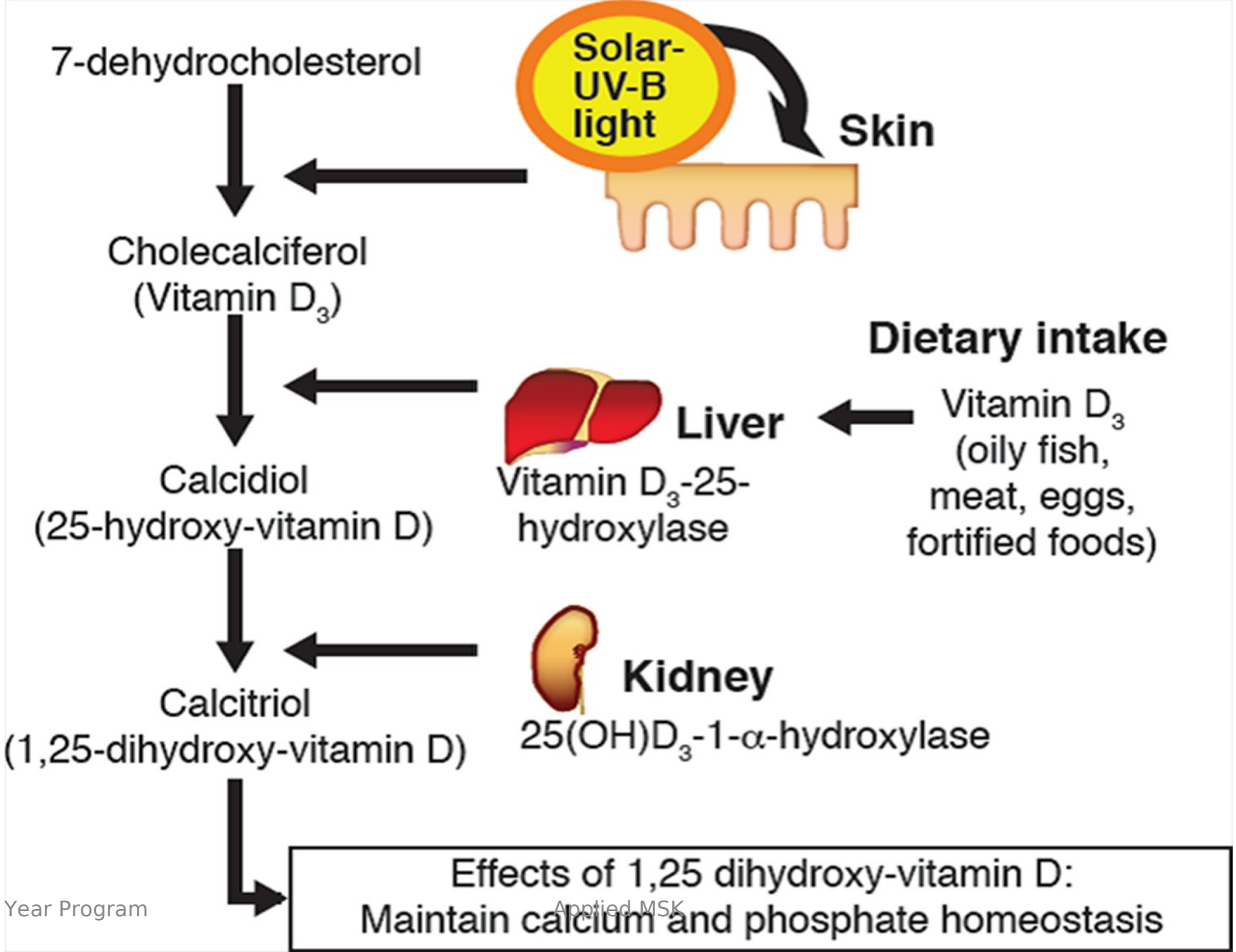


https://www.cancertherapyadvisor.com/wp-content/uploads/sites/12/2019/01/ch4393.fig1_.jpg



http://csls-text3.c.u-tokyo.ac.jp/images/fig/c_fig11_02_lrg.jpg


7-dehydrocholesterol
1
3
Calcidiol
(25-hydroxy-vitamin D)
2


7-dehydrocholesterol
Solar-UV-B light
Skin
Cholecalciferol (Vitamin D_3)
Dietary intake
Liver
Vitamin D_3 (oily fish, meat, eggs, fortified foods)
Calcidiol (25-hydroxy-vitamin D)
Vitamin D_3-25-hydroxylase
Kidney
Calcitriol (1,25-dihydroxy-vitamin D)
25(OH)D_3-1-α-hydroxylase
Effects of 1,25 dihydroxy-vitamin D:
Maintain calcium and phosphate homeostasis

.....

iol is the predominant form of vitamin D in the plasma and the major storage form of the vitamin.

Vitamin D regulation occurs on

.....

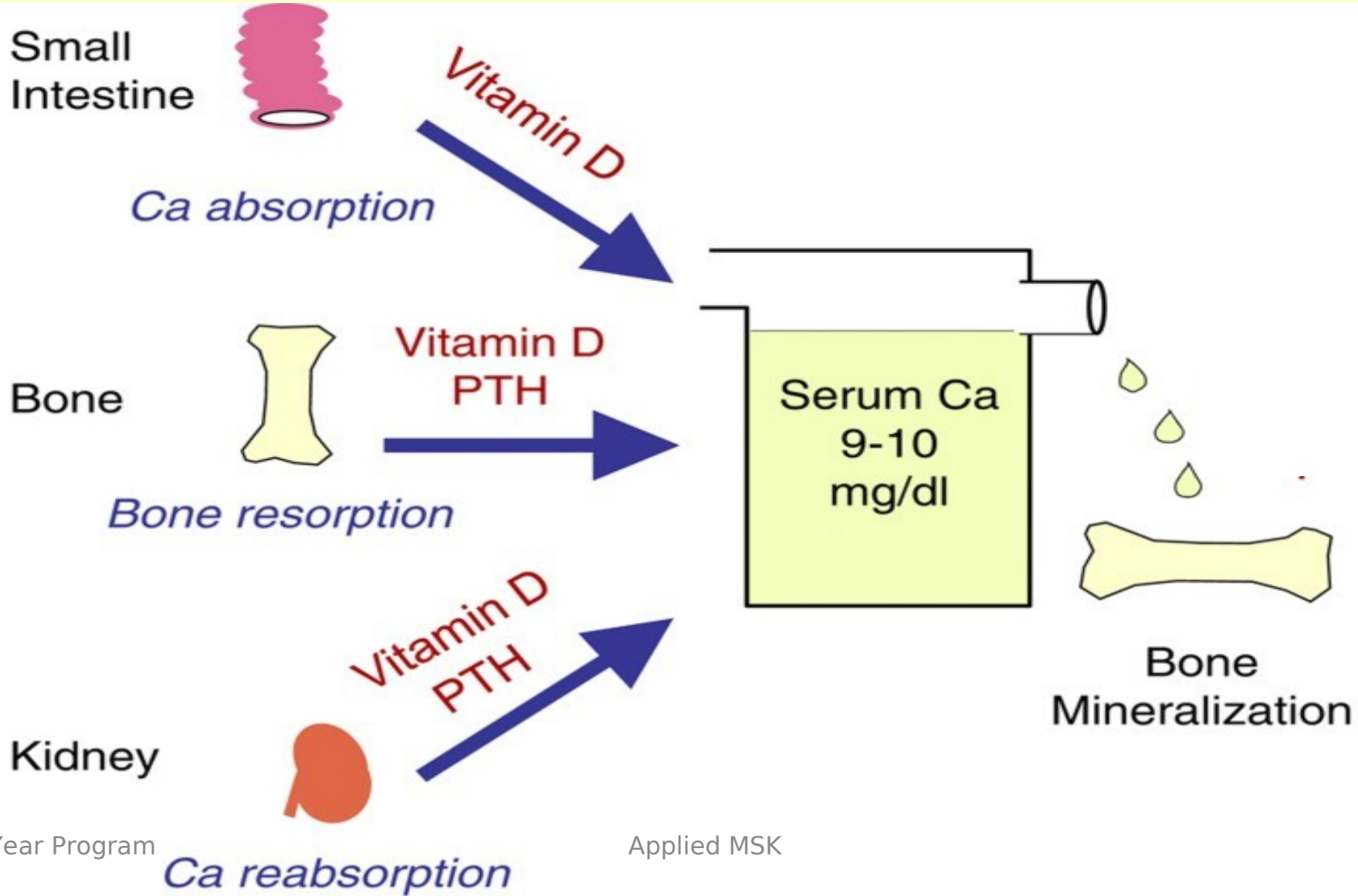
roxylase enzyme

.....

,

increases 1α-hydroxylase activity

Effect of vitamin D on plasma levels of calcium??




many
Thanks!